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Article title

Incidence and relative risk for developing cancers in women with gestational diabetes mellitus: a nationwide cohort study in Taiwan

Running title:

Increased risk of cancer with previous gestational diabetes

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Abbreviations

GDM, gestational diabetes; T2DM, type 2 diabetes; NHIRD, National Health

Insurance Research Database; ICD-9-CM, International Classification of Disease, 9th Revision, Clinical Modification; OPD, outpatient department; AHR, adjusted hazard ratio.

Conflict of interest

The authors declare no conflict of interest.

ABSTRACT

Objectives:

To evaluate the risk of developing cancers, particularly site-specific cancers, in women with gestational diabetes mellitus (GDM) in Taiwan.

Setting:

The National Health Insurance Research Database (NHIRD) of Taiwan.

Participants

This study was conducted using the nationwide data from 2000 to 2013. In total, 1,466,596 pregnant women with admission for delivery were identified. Subjects with GDM consisted of 47,373 women, while the control group consisted of 943,199 women without GDM. The participants were followed from the delivery date to the diagnosis of cancer, death, the last medical claim or the end of follow-up (December 31 2013), whichever came first.

Primary outcome measures:

Patients with a new diagnosis of cancer (ICD-9-CM codes 140–208) recorded in NHRID were identified. The risk of 11 major cancer types was assessed, including cancers of head and neck, digestive organs, lung and bronchus, bone and connective tissue, skin, breast, genital organs, urinary system, brain, thyroid and hematological system.

Results:

The rates of developing cancers were significantly higher in women with GDM compared to non-GDM group (2.24% vs. 1.96%; p<0.001). After adjusting for maternal age at delivery and comorbidities, women with GDM had increased risk of cancers, including cancers of nasopharynx (adjust hazard ratio (AHR), 1.739; 95 % CI, 1.400 to 2.161; p<0.0001), kidney (AHR, 2.169; 95 % CI, 1.428 to 3.293; p=0.0003), lung and bronchus (AHR, 1.372; 95 % CI, 1.044 to 1.803; p=0.0231), breast (AHR, 1.234; 95 % CI, 1.093 to 1.393; p=0.007), and thyroid gland (AHR, 1.389; 95 % CI, 1.121 to 1.721; p=0.0026).

Conclusion: Women with GDM have a higher risk of developing cancers. Cancer screening is warranted in women with GDM. Future research should be aimed to establish whether this association is causal.

Keywords：Gestational diabetes, Cancer, National health insurance research database

Strengths and limitations of this study

- Our study represents the first one to document that women with GDM have a higher risk of developing cancers of nasopharynx, lung and bronchus, and kidney.
- This nationwide population-based cohort study included more than one million women, making selection bias minimal. Furthermore, the use of big data from Taiwan NHIRD also decreased the risk of recall bias which is inherent to self-reporting. Thus, our findings are potentially generalizable.
- The data from NHIRD lack information on other factors that may be associated with GDM and cancer, such as smoking, alcohol consumption, obesity, dietary style, environmental exposure, genetic parameters, and family history of cancers.
- The relatively short follow-up period (6.84±3.05 years) in our study may not have allowed some slow-growing cancers to be detected.

INTRODUCTION

Pregnancy is normally accompanied by insulin resistance, which is facilitated by placental production of diabetogenic hormones. Gestational diabetes mellitus (GDM) develops in pregnant women whose pancreatic islet function is inadequate to overcome the insulin resistance that accompanies pregnancy (1). GDM is associated with adverse outcomes of pregnancy, for example, preeclampsia, macrosomia, and cesarean delivery (1). The prevalence of GDM varies worldwide and among racial and ethnic groups (2), and is generally in parallel with the prevalence of type 2 diabetes (T2DM). Indeed, it has been shown that women diagnosed with GDM are at lifetime risk of developing T2DM subsequently (3). Lately, the prevalence of GDM has been on the rise (4). The reasons for this phenomenon may be an increase in maternal age, obesity issues and a decrease in daily physical activity.

Accumulating lines of evidence have demonstrated an association between T2DM and certain types of cancers. Although the exact causes for this phenomenon are not yet fully understood, chronic hyperinsulinemia which is prompted by insulin resistance has been proposed to be the major channel through which T2DM can trigger tumor growth. Some studies, although not all, suggested that T2DM may contribute to an increased mortality (5). Interestingly, the increase in cancer risk has been found not only in T2DM but also in pre-diabetes (6). GDM is characterized by

hyperglycemia, insulin resistance, hyperinsulinemia and increased levels of Insulin-like growth factor 1 (IGF-1), which can potentially lead to uncontrolled growth of cells and cancer (1, 7). Since GDM has the same characteristics as T2DM and is a predictor for subsequent overt T2DM, it is plausible that GDM may represent a risk factor for the future cancers. Indeed, several studies have been conducted to address whether GDM increases risk of cancer, but yielded mixed results probably because of methodological limitations such as self-reported GDM information, relatively small population and insufficient statistical power resulting from rare occurrence of cancers among young women (7-12). Most previous studies focused on the association between GDM and breast cancer. Only a few have investigated the relationship between GDM and other types of cancers. Moreover, few studies on the association between cancer and GDM have been carried out in Asia-Pacific region where certain types of cancer are particularly prevalent. Therefore, it is unknown whether currently available data can be generalized to different ethnic groups.

The aim of this study was to determine the risk of developing cancers particularly site-specific cancers in women with prior GDM using the National Health Insurance Research Database (NHIRD), which was created by National Health Research Institutes (NHRI) for academic research (13).

MATERIALS AND METHODS

Ethics statement

This study was granted a waiver for the requirement for informed consents by the Institutional Review Board of Chang Gung memorial Hospital (IRB: 103-2572B) because all data in the NHIRD were anonymized and de-identified before release.

Source of data

Data in NHIRD were used. NHIRD contains the registration files and original claim data for reimbursements from the national health insurance (NHI) program of Taiwan; This NHI program was implemented in 1995; and covers 99.5% of the 23 million residents in Taiwan. NHI program offers a comprehensive, unified, and universal health insurance program to all citizens. The coverage includes outpatient service, inpatient care, dental care, childbirth, physical therapy, preventive health care, home care, and rehabilitation for chronic mental illnesses (14). The database contains all dates of inpatient and outpatient services, diagnosis, prescriptions, examinations, operations, and expenditures, and is updated biannually.

Study groups:

This study used data published by the NHRI in Taiwan and covered the years from 2000 to 2013. The diagnostic coding of the NHI in Taiwan was performed according to the International Classification of Disease, 9th Revision, Clinical

Modification (ICD-9-CM) diagnostic criteria.

Inclusion and exclusion criteria:

A total of 1,466,596 pregnant women with admission for delivery were found in the NHIRD between Jan 1, 2002 and Dec 31, 2012. Among these women, we identified 47,373 women who had been diagnosed with gestational diabetes (ICD-9-CM code 648, 250), and had at least 2 consensus diagnoses at prenatal outpatient visits or at least one diagnosis at inpatient admissions during the prenatal period to ensure the validity of diagnosis. (Fig.1). The remaining 943,199 women without GDM, diabetes or malignancy were used as controls. The incidence of GDM was 4.78 in 100 deliveries during the 11-year span (Table 1).

Patients with missing data (n=422,568), history of malignancy (ICD-9-CM codes 140 to 208) (n=9,809), or diabetes (ICD-9-CM codes 250) (n=37,026) two years before pregnancy were excluded. The date of delivery was set as the index date. To avoid inclusion of patients with cancers that arose during or before pregnancy, GDM and control participants were followed for 180 days after delivery until malignancy diagnosis, death, the last medical claim or the end of study follow-up (December 31 2013), whichever came first. We excluded the women with a cancer diagnosis during pregnancy or within 180 days postpartum. (n=778). 5827 patients were also excluded due to loss of follow-up within 180 days after delivery.

Primary outcome

The primary outcome was defined as a new diagnosis of any cancer (ICD-9-CM codes 140–208) recorded in NHRID between January 1, 2002 and December 31, 2013.

Sub-classification of Cancers

We classified cancers into the 11 groups as previously described (12), on basis of the ICD-9-CM (Table 3): cancers of head and neck, digestive organs, lung and bronchus, bone and connective tissue, skin, breast, genital organs, urinary system, brain, thyroid gland and hematological system. Some of these cancers were further sub-classified as follows: The digestive subgroup included cancers of the esophagus, stomach, colon and rectum, liver, biliary system, and pancreas. The genital subgroup included cancers of the cervix uteri, ovary, and uterus. The urinary subgroup included cancers of urinary bladder and kidney. The head and neck subgroup included cancers of oral cavity and pharynx, nasopharynx, larynx, and major salivary glands. The bone and connective tissue subgroup included cancers of bone and sarcoma. The hematological system subgroup included lymphoma and leukemia.

Baseline comorbidities were assessed for 2 years and included hypertension (ICD-9-CM codes 401-405), and dyslipidemia (ICD-9-CM code 272), liver disease (ICD-9-CM codes 070, 571), infertility (ICD-9-CM codes 628), kidney disease

(ICD-9-CM codes 582-3, 585-6, 588).

Statistical analysis

Continuous variables were presented as the mean with SDs. The $\chi 2$ test was used to compare categorical variables, and the differences among continuous variables were compared using the Student's t-test. The proportion of patients with cancer was plotted by Kaplan–Meier curves with log-rank test constructed to compare the cumulative incidence of any type of cancer between subjects with and without GDM. The relative risk of cancer was estimated by Cox proportional regression analysis, which was adjusted for potential confounding variables, such as age and comorbidities. The statistical significance was inferred at a two-sided p value of <0.05. All statistical analyses were performed using the Statistical Analysis Software (SAS) System, V.9.4 (SAS Institute, Cary, North Carolina, USA). Kaplan-Meier curves were plotted using Stata V.12 (Stata Corp, College Station, Texas, USA).

RESULTS

Table 1 lists the clinical characteristics of subjects. Overall, 990,572 women were analyzed. Among them, 47,373 women had GDM. The remaining 943,199 women without GDM served as controls. The average length of follow-up was 6.84±3.05 years, and mean age was 28.97±4.91 years. The incidence of GDM was 4.78% during the 11-year span. Women with GDM had a higher incidence of comorbidities than those in the control group, including hypertension, dyslipidemia, liver disease, infertility and kidney disease (Table 1).

Table 2 shows that the adjusted hazard ratio (AHR) of developing any type of cancer among women with GDM was 1.197 (95% CI, 1.125 to 1.274) compared to women without GDM after adjusting for age and comorbidities.

Patients with GDM were diagnosed with cancer (n=1,063, 2.24%) at a significantly higher rate than those patients without GDM (n=18,444, 1.96%; $p<0.001$). (Table 3). Figure 2 shows the cumulative incidence rates of any type of cancer in patients with or without GDM from the index date until the first occurrence of cancer. The patients with GDM had higher cancer incidence rates compared with those patients without GDM (log-rank test: $p<0.0001$).

Adjusting for maternal age at delivery, and comorbidities, women with a history of GDM had an increased risk of cancers, including cancers of nasopharynx (AHR,

1.739; 95 % CI, 1.400 to 2.161; p<0.0001), kidney (AHR, 2.169; 95 % CI, 1.428 to 3.293, p=0.0003), lung and bronchus (AHR, 1.372; 95 % CI, 1.044 to 1.803; p=0.0231), breast (AHR, 1.234; 95 % CI, 1.093 to 1.393; p=0.0007), and thyroid gland (AHR, 1.389; 95 % CI, 1.121 to 1.721; p=0.0026). (Table 3)

DISCUSSION

The major findings of this study are as follows: [1] GDM is associated with a 19.7% higher risk of developing malignancy. [2] Women with GDM are at a higher risk of developing cancers of nasopharynx, lung and bronchus, kidney, breast, and thyroid glands.

One of our novel findings is that women with GDM are more likely to develop nasopharyngeal cancer (NPC) during the period of follow-up. NPC differs from other head and neck cancers in epidemiology, histology, natural history, and response to treatment. NPC is one of the neoplasms that are linked to infectious agents and displays a distinct racial and geographic distribution. While NPC is rare in Europe and America, it is endemic in Southeastern Asia including Taiwan where Epstein-Barr virus (EBV) infection is prevalent (15). The recrudescence of EBV in immunocompromised patients has been characterized by activating the expression of EBV latency genes, consequently immortalizing the infected cells and leading to carcinogenesis (16). Indeed, the immune dysfunction inherent to T2DM increases the susceptibility to various infections and risk of reactivating latent virus infections as well; eventually contributing to higher rates of mortality (17-20). It is unknown whether GDM, a pre-diabetes condition, is pathogenetically linked to reactivation of EBV infection and subsequent malignant transformation.

Another novel finding in our study is that the risk of developing kidney cancer is significantly higher in women with GDM, compared to those without GDM. The etiology of kidney cancer remains elusive, but smoking, hypertension, obesity, analgesics use, chronic kidney disease (CKD), and genetic defects are potential risk factors (21, 22). Of these factors, obesity and hypertension also characterize GDM (1). Indeed, it has been shown that patients with T2DM have a higher risk of developing kidney cancers (23, 24). In fact, GDM is associated with subsequent development of T2DM and CKD (3, 25). It is unknown whether prevention of CKD would reduce the risk of kidney cancer in women with GDM.

Our study is also the first to demonstrate the association between GDM and lung cancers, which is the most common cancer around the world (26). The prevalence of both lung cancer and GDM has been on the increase in Taiwan and worldwide (4, 27). Whether this association is causal remains to be determined. Importantly, GDM and lung cancer do share common risk factors such as smoking, dietary style, and obesity (26, 28). It is unknown whether modification of these risk factors could impact this association.

In the present study, we also observed a clear association between GDM and breast cancer. Previous studies on the association between GDM and breast cancer have produced mixed results (7-12, 29-34). The reasons for the discrepancy are not

clear. They could be explained by methodological limitations. First, most of these studies were based on self-reported information about GDM (9-11, 29, 31, 32, 34), which is prone to recall bias. Secondly, small sample size and relatively rare occurrence of cancer among young women may result in inadequate statistical power, contributing to inconsistency. In these regards, our big database from Taiwan NHIRD confers an advantage to overcome these methodological limitations.

In agreement with a previous study (8), we showed that GDM was associated with a 38.9% higher risk of developing thyroid cancer. Interestingly, a large study from United States found that the risk of thyroid cancer was significantly increased in women, but not in men, with diabetes (35). Taken together, women with GDM may represent a readily recognizable subgroup that deserves a more intensive surveillance for thyroid cancer.

The elucidation of the relationship between GDM and later cancer risk may not be straightforward. It is conceivable that GDM may impact subsequent cancer risk through certain direct or indirect pathophysiological mechanisms such as hyperglycemia, hyperinsulinemia secondary to insulin resistance and chronic inflammation. Shared risk factors for GDM and cancers can be other explanations, for example smoking, alcohol drinking, obesity, physical inactivity, hypertension and dietary style.

Insulin has mitogenic effects on cells (36). On the other hand, hyperglycemia can induce production of reactive oxygen species (ROS), which can initiate carcinogenesis by damaging cellular DNA (37, 38).

Recently, the role of systemic inflammation in the pathogenesis of GDM has gained more and more attention. Increased circulating levels of interleukin-6 (IL-6) and C-reactive protein (CRP) have been observed in GDM independent of obesity (39, 40), suggesting GDM as a state of low grade inflammation. Inflammation is also a hallmark of cancer and is widely recognized to influence all cancer stages from cell transformation to metastasis (41). Therefore, chronic and systemic inflammation may represent the biological phenomenon linking GDM to cancer development. Future investigations on the role of low-grade inflammation in GDM may help identify biomarkers that can better predict, diagnose and monitor the evolution of GDM. Moreover, specific inflammatory pathways may represent novel targets for treatment and prevention of long-term adverse outcomes of GDM, including cancer development.

There were several strengths in this study. First, this is population-based study with a large nationally representative sample from Taiwan NHIRD, thus maing selection bias minimized. Secondly, the use of NHIRD reduced the potential recall bias that is inherent to self-reporting.

Limitations of this study included the lack of information about the histology and staging of cancer. Secondly, our study did not have information about potential confounders such as dietary, obesity, physical activity, smoking, alcohol consumption, environmental exposure and genetic parameters. Third, the follow-up period may not be long enough to allow detection of cancers in young women.

CONCLUSIONS

This population-based analysis of Taiwan NHIRD showed that women with GDM in Taiwan have an increased risk of developing malignancy including cancers of nasopharynx, lung, kidney, breast, and thyroid gland. Prevention of GDM may be an important strategy in curbing the development of certain types of cancers in the future. Our study also highlights under-recognized cancers in women with GDM that warrants further investigations to develop different surveillance strategies for cancer development in GDM patients in different ethnic groups.

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Contributors

YSP proposed and designed the study. YSP also drafted the manuscript. MHT supervised the study and critically edited the manuscript; and finally approved the version to be submitted. JRL designed the study's analytic strategy and conducted the data analysis. BHC and CH contributed to study design and prepare the Methods and the Discussion sections of the text, YHL and CHS conducted literature review. All authors have read and approved the final manuscript.

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Competing interests

The authors declare no conflict of interest.

Ethics approval

This study protocol was approved by the institutional review board of Chang Gung Medical Foundation (IRB 103-2572B).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

REFERENCES

1. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010;33:676.
2. Dornhorst A, Paterson CM, Nicholls JS, et al. High prevalence of gestational diabetes in women from ethnic minority groups. *Diabet Med* 1992;9:820-5.
3. Chodick G, Elchalal U, Sella T, et al. The risk of overt diabetes mellitus among women with gestational diabetes: a population-based study. *Diabet Med* 2010;27:779-85
4. Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. *Diabetes Care* 2007;30(Suppl 2):P141-6 ·
5. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 2008;300:2754-64.
6. Stattin P, Björ O, Ferrari P, et al. Prospective study of hyperglycemia and cancer risk. *Diabetes Care* 2007;30:561-7.
7. Tong GX, Cheng J, Chai J, et al. Association between gestational diabetes mellitus and subsequent risk of cancer: a systematic review of epidemiological studies.

Asian Pac *J Cancer Prev* 2014;15:4265-9.

8. Bejaimal SA, Wu CF, Lowe J, et al. Short-term risk of cancer among women with previous gestational diabetes: a population-based study. *Diabet Med* 2016;33:39-46.
9. Powe CE, Tobias DK, Michels KB, et al. History of Gestational Diabetes Mellitus and Risk of Incident Invasive Breast Cancer among Parous Women in the Nurses' Health Study II Prospective Cohort. *Cancer Epidemiol Biomarkers Prev* 2017;26:321-7.
10. Park YM, O'Brien KM, Zhao S, et al. Gestational diabetes mellitus may be associated with increased risk of breast cancer. *Br J Cancer* 2017;116:960-3.
11. Dawson SI. Long-term risk of malignant neoplasm associated with gestational glucose intolerance. *Cancer* 2004;100,149-55.
12. Sella T, Chodick G, Barchana M, et al. Gestational diabetes and risk of incident primary cancer: a large historical cohort study in Israel. *Cancer Causes Control* 2011;22,1513-20.
13. Chen YC, Yeh, H, Wu JC, et al. Taiwan's National Health Insurance Research Database: Administrative health care database as study object in bibliometrics. *Scientometrics* 2011,86,365-80.
14. Hsing AW, Ioannidis JP. Nationwide population science: lessons from the Taiwan

National Health Insurance Research Database. *JAMA Intern Med* 2015;175:1527-9.

15. Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. *Semin Cancer Biol* 2002;12:421-9.

16. Cohen JI. Epstein-Barr virus infection. *N Engl J Med* 2000;343:481-92.

17. Plouffe JF, Silva J, Jr, Fekety R, et al. Cell-mediated immunity in diabetes mellitus. *Infect Immun* 1978;21:425-9.

18. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM) FEMS *Immunol Med Microbiol*. 1999;26:259-65.

19. Berrou J, Fougeray S, Venot M, et al. Natural killer cell function, an important target for infection and tumor protection, is impaired in type 2 diabetes. *PLoS One* 2013;8:e62418.

20. Kumar M, Roe K, Nerurkar PV, et al. Impaired virus clearance, compromised immune response and increased mortality in type 2 diabetic mice infected with West Nile virus. *PLoS One* 2012;7:e44682.

21. Ljungberg B, Campbell SC, Choi HY, et al. The epidemiology of renal cell carcinoma. *Eur Urol* 2011;60:615-21.

22. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. *Nat Rev Urol* 2010;7:245-57.

23. Larsson SC, Wolk A. Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. *Diabetologia* 2011;54:1013-8.

24. Tseng CH. Type 2 Diabetes Mellitus and Kidney Cancer Risk: A Retrospective Cohort Analysis of the National Health Insurance. *PLoS One* 2015;11;10:e0142480.

25. Dehmer EW, Phadnis MA, Gunderson EP, et al. Association Between Gestational Diabetes and Incident Maternal CKD: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Kidney Dis* 2018;71:112-22.

26. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med* 2011;32:605-44.

27. Tseng CH. Diabetes but not insulin increases the risk of lung cancer: a Taiwanese population-based study. *PLoS One* 2014;9:e101553.

28. Solomon CG, Willett WC, Carey VJ, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. *JAMA* 1997;278:1078-83.

29. Troisi R, Weiss HA, Hoover RN, et al. Pregnancy characteristics and maternal risk of breast cancer. *Epidemiology* 1998;9,641-7.

30. Cnattingius S, Torrang A, Ekbom A, et al. Pregnancy characteristics and maternal risk of breast cancer. *JAMA* 2005;294,2474-80.

31. Brasky TM, Li Y, Jaworowicz DJ Jr, et al. Pregnancy-related characteristics and

breast cancer risk. *Cancer Causes Control* 2013;24,1675-85.

32. Lawlor DA, Smith GD, Ebrahim S. Hyperinsulinaemia and increased risk of breast cancer: findings from the British Women's Heart and Health Study. *Cancer Causes Control* 2004;15,267-75.

33. Perrin MC, Terry MB, Kleinhaus K, et al. Gestational diabetes and the risk of breast cancer among women in the Jerusalem Perinatal Study. *Breast Cancer Res Treat* 2008;108,129-35.

34. Rollison DE, Giuliano AR, Sellers TA, et al. Population-based case-control study of diabetes and breast cancer risk in Hispanic and non-Hispanic White women living in US southwestern states. *Am J Epidemiol* 2008;167,447-56.

35. Aschebrook-Kilfoy B, Sabra MM, Brenner A, et al. Diabetes and thyroid cancer risk in the National Institutes of Health-AARP Diet and Health Study. *Thyroid* 2011;21:957-63.

36. Vigneri P, Frasca F, Siacca L, et al. Diabetes and cancer. *Endocr. Relat. Cancer* 2009;16,1103-23.

37. Chandrasekaran K, Swaminathan K, Chatterjee S, et al. Apoptosis in hepG2 cells exposed to high glucose. *Toxicol. In Vitro* 2010;24,387-96.

38. Zhang Y, Zhou J, Wang T, Cai T. High level glucose increases mutagenesis in human lymphoblastoid cells. *Int. J. Biol. Sci.* 2007;3,275-9.

39. Ategbo JM, Grissa O, Yessoufou A, et al. Modulation of adipokines and cytokines in gestational diabetes and macrosomia. *J Clin Endocrinol Metab* 2006;91:4137e43.

40. Wolf M, Sandler L, Hsu K, et al. First-trimester C-reactive protein and subsequent gestational diabetes. *Diabetes Care* 2003;26:819-24.

41. Leonardi GC, Accardi G, Monastero R, et al. Ageing: from inflammation to cancer. *Immun Ageing* 2018;15:1.

Table 1 Baseline characteristics

	Pregnancy women with GDM		Pregnancy women without GDM		P value
Number of population, n (%)	47373	(4.78)	943199	(95.22)	
Age, y, mean±SD		31.61±4.54		28.83±4.89	<.0001
Age at pregnancy, n (%)					<.0001
≤ 20	407	(0.86)	45942	(4.87)	
21-30	18617	(39.30)	558108	(59.17)	
31-40	27203	(57.42)	329929	(34.98)	
41-50	1146	(2.42)	9220	(0.98)	
Comorbidity, n (%)					
Hypertension (icd9 401-405)	1479	(3.12)	7743	(0.82)	<.0001
Dyslipidemia (icd9 272)	1132	(2.39)	8197	(0.87)	<.0001
Liver disease (icd9 070, 571)	3165	(6.68)	44509	(4.72)	<.0001
Infertility, female (icd9 628)	8001	(16.89)	94405	(10.01)	<.0001
Kidney disease (icd9 582-3, 585-6, 588)	51	(0.11)	626	(0.07)	0.0008

SD=Standard Deviation

Table 2 Hazard ratio (HR) of developing cancer in relation to baseline characteristics of study participants:

	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Patients				
GDM	1.421 (1.336-1.512)	<0.0001	1.197 (1.125-1.274)	0.0012
Non-GDM	1.0 (ref)		1.0 (ref)	
Age				
≤ 20	1.0 (ref)		1.0 (ref)	
21-30	1.627 (1.488-1.779)	<0.0001	1.581 (1.446-1.729)	<0.0001
31-40	2.843 (2.600-3.109)	<0.0001	2.678 (2.448-2.930)	<0.0001
41-50	4.883 (4.291-5.556)	<0.0001	4.479 (3.933-5.100)	<0.0001
Comorbidity, n (%)				
Hypertension (icd9 401-405)	1.471 (1.291-1.677)	<0.0001	1.114 (0.976-1.272)	0.1101
Dyslipidemia (icd9 272)	1.866 (1.648-2.113)	<0.0001	1.395 (1.229-1.583)	<0.0001
Liver disease (icd9 070, 571)	1.573 (1.486-1.665)	<0.0001	1.432 (1.351-1.517)	<0.0001
Infertility, female (icd9 628)	1.397 (1.340-1.457)	<0.0001	1.185 (1.136-1.236)	<0.0001
Kidney disease (icd9 582-3, 585-6, 588)	2.077 (1.403-3.073)	0.0003	1.623 (1.095-2.404)	0.0159

Model was adjusted for age, hypertension, dyslipidemia, liver disease, infertility, and kidney disease; HR=Hazard Ratio.

Table 3 Hazard ratio (HR) of the first cancer diagnosis between GDM group and non GDM groups

(ICD-9 code)	Women with GDM (N=47373)		Women without GDM (N=943199)		Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Head and neck								
Oral & pharynx (140-1、143-6、148-9)*	19	(0.04)	389	(0.04)	1.230 (0.776-1.950)	0.380	1.105 (0.695-1.759)	0.6724
Nasopharynx (147)*	90	(0.19)	1151	(0.12)	1.897 (1.530-2.351)	<.0001	1.739 (1.400-2.161)	<.0001
Larynx (161)*	5	(0.01)	84	(0.01)	1.494 (0.605-3.686)	0.384	1.562 (0.628-3.877)	0.3379
Major salivary gland (142)*	5	(0.01)	69	(0.01)	1.774 (0.715-4.402)	0.216	1.476 (0.591-3.688)	0.4044
Digestive system								
Esophagus (150)*	3	(0.01)	88	(0.01)	0.748 (0.237-2.363)	0.620	0.554 (0.175-1.756)	0.3157
Stomach (151)*	18	(0.04)	256	(0.03)	1.703 (1.056-2.749)	0.029	1.322 (0.816-2.142)	0.2570
Colorectum (153-4)*	100	(0.21)	1705	(0.18)	1.420 (1.160-1.738)	0.0007	1.180 (0.963-1.447)	0.1099
Liver (155)*	87	(0.18)	1393	(0.15)	1.504 (1.211-1.868)	0.0002	1.242 (0.998-1.545)	0.0521
Biliary system (156)*	4	(0.01)	43	(<0.01)	2.329 (0.835-6.496)	0.106	1.954 (0.692-5.516)	0.2058
Pancreas (157)*	17	(0.04)	314	(0.03)	1.316 (0.808-2.145)	0.270	1.072(0.655-1.755)	0.7807
Genital system								
Cervix uteri (180)*	37	(0.08)	962	(0.10)	0.925 (0.666-1.285)	0.643	0.903 (0.649-1.256)	0.5438
Uterus (179,182)*	42	(0.09)	803	(0.09)	1.323 (0.970-1.805)	0.077	1.051 (0.769-1.437)	0.7534
Ovary (183)*	50	(0.11)	1146	(0.12)	1.061 (0.800-1.409)	0.680	0.963 (0.724-1.280)	0.7928
Urinary system								
Urinary bladder (188)*	9	(0.02)	162	(0.02)	1.387 (0.709-2.715)	0.340	1.034 (0.525-2.033)	0.9236
Kidney (189)*	25	(0.05)	245	(0.03)	2.573 (1.704-3.885)	<.0001	2.169 (1.428-3.293)	0.0003
Hematological system								
Leukemia (204-8)*	11	(0.02)	359	(0.04)	0.742 (0.407-1.352)	0.329	0.735 (0.402-1.344)	0.3169
Lymphoma (200-3)*	19	(0.04)	596	(0.06)	0.771 (0.488-1.217)	0.264	0.774 (0.489-1.226)	0.2754
Bone and connective tissue								
Bone (170)*	4	(0.01)	96	(0.01)	0.992 (0.365-2.699)	0.988	0.977 (0.357-2.677)	0.9646
Sarcoma (171)*	3	(0.01)	175	(0.02)	0.412 (0.132-1.289)	0.128	0.387 (0.123-1.217)	0.1045
Lung and bronchus (162)*	56	(0.12)	846	(0.09)	1.666 (1.271-2.184)	0.0002	1.372 (1.044-1.803)	0.0231
Skin (173)*	15	(0.03)	201	(0.02)	1.834 (1.085-3.101)	0.024	1.664 (0.980-2.825)	0.0594
Breast (174)*	284	(0.60)	4373	(0.46)	1.654 (1.467-1.866)	<.0001	1.234 (1.093-1.393)	0.0007
Brain (191)*	19	(0.04)	331	(0.04)	1.382 (0.870-2.195)	0.170	1.232 (0.772-1.968)	0.3818
Thyroid (193)*	91	(0.19)	1423	(0.15)	1.582 (1.279-1.956)	<.0001	1.389 (1.121-1.721)	0.0026
Other sites	74	(0.16)	1435	(0.15)	1.046 (0.799-1.370)	0.743	0.967 (0.737-1.269)	0.8104
Total (140-208)	1063	(2.24)	18444	(1.96)	1.421 (1.336-1.512)	<.0001	1.197 (1.125-1.274)	<.0001

LEGENDS:

Figure 1: Flow chart for selection of study population

Figure 2: The cumulative incidence rates of any type of cancer in patients with or without GDM from the index date until the first occurrence of the cancer using Kaplan-Meier methods.

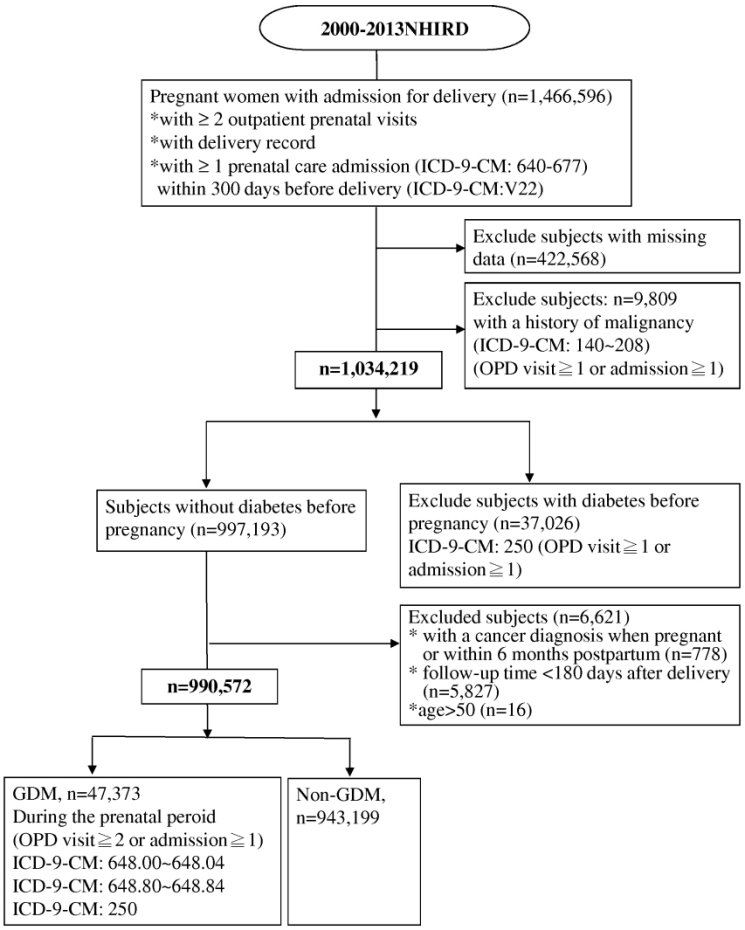

Figure 1

209x297mm (300 x 300 DPI)

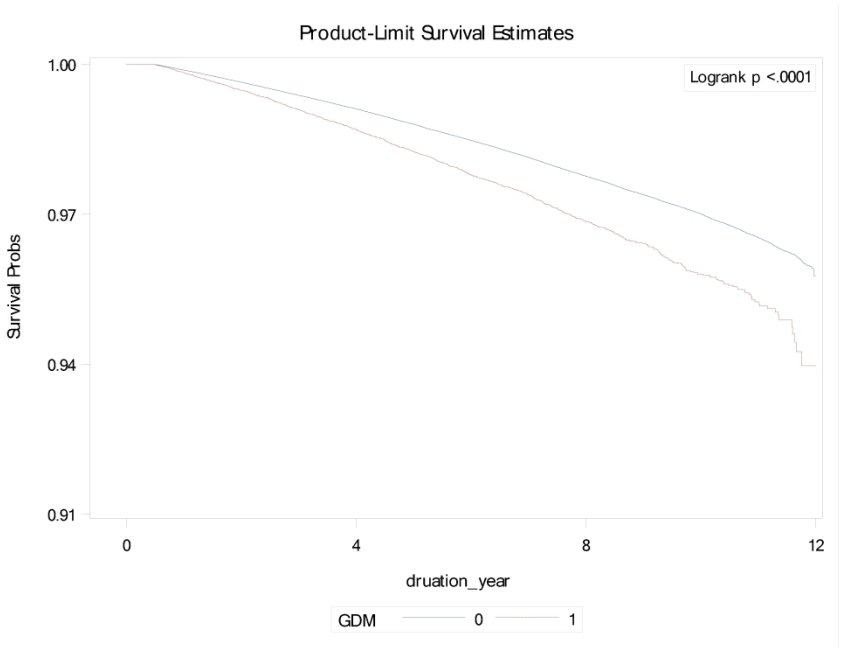

Figure 2

297x209mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10-11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-12
Bias	9	Describe any efforts to address potential sources of bias	10-12
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	10, See Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13,28-29
		(b) Indicate number of participants with missing data for each variable of interest	13
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-14, 28-30
		(*b*) Report category boundaries when continuous variables were categorized	13, 28
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13-14, 29-30
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13, See Fig 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Incidence and relative risk for developing cancers in women with gestational diabetes mellitus: a nationwide cohort study in Taiwan

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Article title

Incidence and relative risk for developing cancers in women with gestational diabetes mellitus: a nationwide cohort study in Taiwan

Running title:

Increased risk of cancer with previous gestational diabetes

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Abbreviations

GDM, Gestational diabetes mellitus; T2DM, type 2 diabetes mellitus; NHIRD, National Health Insurance Research Database; ICD-9-CM, International Classification of Disease, 9th Revision, Clinical Modification; OPD, outpatient department; AHR, adjusted hazard ratio.

Conflict of interest

The authors declare no conflict of interest.

ABSTRACT

Objectives:

To evaluate the risk of developing cancers, particularly site-specific cancers, in women with gestational diabetes mellitus (GDM) in Taiwan.

Setting:

The National Health Insurance Research Database (NHIRD) of Taiwan.

Participants

This study was conducted using the nationwide data from 2000 to 2013. In total, 1,466,596 pregnant women with admission for delivery were identified. Subjects with GDM consisted of 47,373 women, while the non-exposed group consisted of 943,199 women without GDM. The participants were followed from the delivery date to the diagnosis of cancer, death, the last medical claim or the end of follow-up (December 31 2013), whichever came first.

Primary outcome measures:

Patients with a new diagnosis of cancer (ICD-9-CM codes 140–208) recorded in NHIRD were identified. The risk of 11 major cancer types was assessed, including cancers of head and neck, digestive organs, lung and bronchus, bone and connective tissue, skin, breast, genital organs, urinary system, brain, thyroid gland, and hematological system.

Results:

The rates of developing cancers were significantly higher in women with GDM compared to non-GDM group (2.24% vs. 1.96%; p<0.001). After adjusting for maternal age at delivery and comorbidities, women with GDM had increased risk of cancers, including cancers of nasopharynx (adjust hazard ratio (AHR), 1.739; 95 % CI, 1.400 to 2.161; p<0.0001), kidney (AHR, 2.169; 95 % CI, 1.428 to 3.293; p=0.0003), lung and bronchus (AHR, 1.372; 95 % CI, 1.044 to 1.803; p=0.0231), breast (AHR, 1.234; 95 % CI, 1.093 to 1.393; p=0.007), and thyroid gland (AHR, 1.389; 95 % CI, 1.121 to 1.721; p=0.0026).

Conclusion:

Women with GDM have a higher risk of developing cancers. Cancer screening is warranted in women with GDM. Future research should be aimed to establish whether this association is causal.

Keywords：Gestational diabetes, Cancer, National health insurance research database

Strengths and limitations of this study

- Our study represents the first one to document that women with GDM have a higher risk of developing cancers of nasopharynx, lung and bronchus, and kidney.
- This nationwide population-based cohort study included more than one million women, making selection bias minimal.
- The use of big data from Taiwan NHIRD also decreased the risk of recall bias which is inherent to self-reporting, thus making our findings potentially generalizable.
- The data from NHIRD lack information on other factors that may be associated with GDM and cancer, such as smoking, alcohol consumption, obesity, dietary style, environmental exposure, genetic parameters, subtypes of cancer, and family history of cancers.
- The relatively short follow-up period (6.84±3.05 years) in our study may not have allowed some slow-growing cancers to be detected.

INTRODUCTION

Pregnancy is normally accompanied by insulin resistance, which is facilitated by placental production of diabetogenic hormones. Gestational diabetes mellitus (GDM) develops in pregnant women whose pancreatic islet function is inadequate to overcome the insulin resistance that accompanies pregnancy (1). GDM is associated with adverse outcomes of pregnancy, for example, preeclampsia, macrosomia, and cesarean delivery (1). The prevalence of GDM varies worldwide and among racial and ethnic groups (2), and is generally in parallel with the prevalence of type 2 diabetes (T2DM). Indeed, it has been shown that women diagnosed with GDM are at lifetime risk of developing T2DM subsequently (3). Lately, the prevalence of GDM has been on the rise (4). The reasons for this phenomenon may be an increase in maternal age, obesity issues and a decrease in daily physical activity.

Accumulating lines of evidence have demonstrated an association between T2DM and certain types of cancers. Although the exact causes for this phenomenon are not yet fully understood, chronic hyperinsulinemia which is prompted by insulin resistance has been proposed to be the major channel through which T2DM can trigger tumor growth. Some studies, although not all, suggested that T2DM may contribute to an increased mortality (5). Interestingly, the increase in cancer risk has been found not only in T2DM

but also in pre-diabetes (6). GDM is characterized by hyperglycemia, insulin resistance, hyperinsulinemia and increased levels of Insulin-like growth factor 1 (IGF-1), which can potentially lead to uncontrolled growth of cells and cancer (1, 7). Since GDM has the same characteristics as T2DM and is a predictor for subsequent overt T2DM, it is plausible that GDM may represent a risk factor for the future cancers. Indeed, several studies have been conducted to address whether GDM increases risk of cancer, but yielded mixed results probably because of methodological limitations such as self-reported GDM information, relatively small population and insufficient statistical power resulting from rare occurrence of cancers among young women (7-13).

Most previous studies focused on the association between GDM and breast cancer. Only a few have investigated the relationship between GDM and other types of cancers. Moreover, few studies on the association between cancer and GDM have been carried out in Asia-Pacific region where certain types of cancer are particularly prevalent. Therefore, it is unknown whether currently available data can be generalized to different ethnic groups.

The aim of this study was to determine the risk of developing cancers particularly site-specific cancers in women with prior GDM using the National Health Insurance Research Database (NHIRD), which was created by National Health Research Institutes

(NHRI) for academic research (14).

MATERIALS AND METHODS

Ethics statement

This study was granted a waiver for the requirement for informed consents by the Institutional Review Board of Chang Gung memorial Hospital (IRB: 103-2572B) because all data in the NHIRD were anonymized and de-identified before release.

Source of data

Data in NHIRD were used. NHIRD contains the registration files and original claim data for reimbursements from the national health insurance (NHI) program of Taiwan; This NHI program was implemented in 1995; and covers 99.5% of the 23 million residents in Taiwan. NHI program offers a comprehensive, unified, and universal health insurance program to all citizens. The coverage includes outpatient service, inpatient care, dental care, childbirth, physical therapy, preventive health care, home care, and rehabilitation for chronic mental illnesses (15). The database provides all dates of inpatient and outpatient services, diagnosis, prescriptions, examinations, operations, and expenditures, and is updated biannually.

Patient and public involvement

In the present study, we used NHIRD, which is the data of insurance claims with anonymised identifications. No patients or public were involved.

Study groups:

This study used data published by the NHRI in Taiwan and covered the years from 2000 to 2013. The diagnostic coding of the NHI in Taiwan was performed according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic criteria.

Inclusion and exclusion criteria:

A total of 1,466,596 pregnant women with admission for delivery were found in the NHIRD between Jan 1, 2000 and Dec 31, 2013 (Figure 1). Subjects were traced back 2 years before delivery to identify if there was a past history of malignancy or diabetes and assess baseline comorbidities which may confound the association between GDM and malignancy. In this context, women with admission for delivery between Jan 1, 2002 and Dec 31, 2012 were further analyzed to avoid pre-existing malignancy and ensure adequate period of time in follow-up. Among these women, we identified 47,373 women who had been diagnosed with gestational diabetes (ICD-9-CM code 648, 250), and had at least 2 consensus diagnoses at prenatal outpatient visits or at least one diagnosis at inpatient admissions during the prenatal period to ensure the validity of diagnosis. (Fig.1). The remaining 943,199 women without GDM, diabetes or malignancy were used

as the non-exposed group. The incidence of GDM was 4.78 in 100 deliveries during the 11-year span (Table 1).

Those women who were not admitted for delivery within the time frame between Jan 1, 2002 and Dec 31, 2012 were excluded (n=422,568). Subjects with a history of malignancy (ICD-9-CM codes 140 to 208) (n=9,809) two years before delivery, or diabetes (ICD-9-CM codes 250) (n=37,026) before pregnancy were excluded. The date of delivery was set as the index date. To avoid inclusion of patients with cancers that arose during or before pregnancy, GDM and the non-exposed participants were followed for 180 days after delivery until malignancy diagnosis, death, the last medical claim or the end of study follow-up (December 31, 2013), whichever came first. We excluded the women with a cancer diagnosis during pregnancy or within 180 days postpartum. (n=778). 5,827 patients were also excluded due to loss of follow-up within 180 days after delivery.

Primary outcome

The primary outcome was defined as a new diagnosis of any cancer (ICD-9-CM codes 140–208) recorded in NHIRD between Jan 1, 2002 and Dec 31, 2013.

Sub-classification of Cancers

We classified cancers into the 11 groups as previously described (12), on basis of the

ICD-9-CM: cancers of head and neck, digestive organs, lung and bronchus, bone and connective tissue, skin, breast, genital organs, urinary system, brain, thyroid gland, and hematological system.

Baseline comorbidities were assessed for 2 years and included hypertension (ICD-9-CM codes 401-405), and dyslipidemia (ICD-9-CM code 272), liver disease (ICD-9-CM codes 070, 571), infertility (ICD-9-CM codes 628), and kidney disease (ICD-9-CM codes 582-3, 585-6, 588). These comorbidities were selected because they have been shown to be associated with both GDM and risk of cancers (16-25).

Statistical analysis

Continuous variables were presented as the mean with SDs. The $\chi 2$ test was used to compare categorical variables, and the differences among continuous variables were compared using the Student's t-test. The proportion of patients with cancer was plotted by Kaplan–Meier curves with log-rank test constructed to compare the cumulative incidence of any type of cancer between subjects with and without GDM. The hazard ratio of cancer was estimated by Cox proportional regression analysis, which was adjusted for potential confounding variables, such as age and comorbidities. The predictors satisfied the proportional hazard assumption in Cox model. The statistical significance was inferred at a two-sided p value of <0.05. All statistical analyses were

performed using the Statistical Analysis Software (SAS) System, V.9.4 (SAS Institute, Cary, North Carolina, USA). Kaplan-Meier curves were plotted using Stata V.12 (Stata Corp, College Station, Texas, USA).

RESULTS

Table 1 lists the clinical characteristics of subjects. Overall, 990,572 women were analyzed. Among them, 47,373 women had GDM. The remaining 943,199 women without GDM served as the non-exposed group. The average length of follow-up was 6.84±3.05 years, and mean age was 28.97±4.91 years. The incidence of GDM was 4.78% during the 11-year span. Women with GDM had a higher rate of comorbidities than those in the non-exposed group, including hypertension, dyslipidemia, liver disease, infertility and kidney disease (Table 1).

Table 2 shows that the adjusted hazard ratio (AHR) of developing any type of cancer among women with GDM was 1.197 (95% CI, 1.125 to 1.274) compared to women without GDM after adjusting for age and comorbidities.

Patients with GDM were diagnosed with cancer (n=1,063, 2.24%) at a significantly higher rate than those without GDM (n=18,444, 1.96%; p<0.001) (Table 3). Figure 2 shows the cumulative incidence rates of any type of cancer in patients with or without

GDM from the index date until the first occurrence of cancer. The patients with GDM had higher cancer incidence rates compared with those patients without GDM (log-rank test: $p<0.0001$).

Adjusting for maternal age at delivery, and comorbidities, women with a history of GDM had an increased risk of cancers, including cancers of nasopharynx (AHR, 1.739; 95 % CI, 1.400 to 2.161; $p<0.0001$), kidney (AHR, 2.169; 95 % CI, 1.428 to 3.293, $p=0.0003$), lung and bronchus (AHR, 1.372; 95 % CI, 1.044 to 1.803; $p=0.0231$), breast (AHR, 1.234; 95 % CI, 1.093 to 1.393; $p=0.0007$), and thyroid gland (AHR, 1.389; 95 % CI, 1.121 to 1.721; $p=0.0026$). (Table 3)

DISCUSSION

The major findings of this study are as follows: [1] GDM is associated with a 19.7% higher risk of developing malignancy. [2] Women with GDM are at a higher risk of developing cancers of nasopharynx, lung and bronchus, kidney, breast, and thyroid glands.

One of our novel findings is that women with GDM are more likely to develop nasopharyngeal cancer (NPC) during the period of follow-up. NPC differs from other head and neck cancers in epidemiology, histology, natural history, and response to treatment. NPC is one of the neoplasms that are linked to infectious agents and displays a distinct racial and geographic distribution. While NPC is rare in Europe and America, it is endemic in Southeastern Asia including Taiwan where Epstein-Barr virus (EBV) infection is prevalent (26). The recrudescence of EBV in immunocompromised patients has been characterized by activating the expression of EBV latency genes, consequently immortalizing the infected cells and leading to carcinogenesis (27). Indeed, the immune dysfunction inherent to T2DM increases the susceptibility to various infections and risk of reactivating latent virus infections as well; eventually contributing to higher rates of mortality (28-31). It is unknown whether GDM, a pre-diabetes condition, is pathogenetically linked to reactivation of EBV infection and subsequent malignant

transformation. It is also unknown whether shared environmental risk factors and genetic susceptibility can be other explanations.

Another novel finding in our study is that the risk of developing kidney cancer is significantly higher in women with GDM, compared to those without GDM. The etiology of kidney cancer remains elusive, but smoking, hypertension, obesity, analgesics use, chronic kidney disease (CKD), and genetic defects are potential risk factors (32, 33). Of these factors, obesity and hypertension also characterize GDM (1). Indeed, it has been shown that patients with T2DM have a higher risk of developing kidney cancers (34, 35). In fact, GDM is associated with subsequent development of T2DM and CKD (3, 25). It is unknown whether prevention of CKD would reduce the risk of kidney cancer in women with GDM.

Our study is also the first to demonstrate the association between GDM and lung cancers, which is the most common cancer around the world (36). The prevalence of both lung cancer and GDM has been on the increase in Taiwan and worldwide (4, 37). Whether this association is causal remains to be determined. Importantly, GDM and lung cancer do share common risk factors such as smoking, dietary style, and obesity (36, 38). It is unknown whether modification of these risk factors could impact this association.

In the present study, we also observed a clear association between GDM and breast

cancer. Previous studies on the association between GDM and breast cancer have produced mixed results (7-13, 39-44). The reasons for the discrepancy are not clear. They could be explained by methodological limitations. First, most of these studies were based on self-reported information about GDM (9-11, 39, 41, 42, 44), which is prone to recall bias. Secondly, small sample size and relatively rare occurrence of cancer among young women may result in inadequate statistical power, contributing to inconsistency. In these regards, our big database from Taiwan NHIRD confers an advantage to overcome these methodological limitations.

In agreement with a previous study (8), we showed that GDM was associated with a 38.9% higher risk of developing thyroid cancer. Interestingly, a large study from United States found that the risk of thyroid cancer was significantly increased in women, but not in men, with diabetes (45). Taken together, women with GDM may represent a readily recognizable subgroup that deserves a more intensive surveillance for thyroid cancer.

The elucidation of the relationship between GDM and later cancer risk may not be straightforward. It is conceivable that GDM may impact subsequent cancer risk through certain direct or indirect pathophysiological mechanisms such as hyperglycemia, hyperinsulinemia secondary to insulin resistance and chronic inflammation. Shared risk factors for GDM and cancers can be other explanations, for example smoking, alcohol

drinking, obesity, physical inactivity, hypertension and dietary style.

Insulin has mitogenic effects on cells (46). On the other hand, hyperglycemia can induce production of reactive oxygen species (ROS), which can initiate carcinogenesis by damaging cellular DNA (47, 48).

Recently, the role of systemic inflammation in the pathogenesis of GDM has gained more and more attention. Increased circulating levels of interleukin-6 (IL-6) and C-reactive protein (CRP) have been observed in GDM independent of obesity (49, 50), suggesting GDM as a state of low grade inflammation. Inflammation is also a hallmark of cancer and is widely recognized to influence all cancer stages from cell transformation to metastasis (51). Therefore, chronic and systemic inflammation may represent the biological phenomenon linking GDM to cancer development. Future investigations on the role of low-grade inflammation in GDM may help identify biomarkers that can better predict, diagnose and monitor the evolution of GDM. Moreover, specific inflammatory pathways may represent novel targets for treatment and prevention of long-term adverse outcomes of GDM, including cancer development.

There were several strengths in this study. First, this is population-based study with a large nationally representative sample from Taiwan NHIRD, thus making selection bias minimized. Secondly, the use of NHIRD reduced the potential recall bias that is inherent

to self-reporting.

Limitations of this study included the lack of information about parity, multiple GDM pregnancy and the histology, subtype and staging of cancer. Secondly, our study did not have information about potential confounders such as dietary, obesity, physical activity, smoking, alcohol consumption, environmental exposure, and genetic parameters. Third, the follow-up period may not be long enough to allow detection of cancers in young women.

CONCLUSIONS

This population-based analysis of Taiwan NHIRD showed that women with GDM in Taiwan have an increased risk of developing malignancy including cancers of nasopharynx, lung, kidney, breast, and thyroid gland. Prevention of GDM may be an important strategy in curbing the development of certain types of cancers in the future. Our study also highlights under-recognized cancers in women with GDM that warrants further investigations to develop different surveillance strategies for cancer development in GDM patients in different ethnic groups.

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Contributors

YSP proposed and designed the study. YSP also drafted the manuscript. MHT supervised the study and critically edited the manuscript; and finally approved the version to be submitted. JRL designed the study's analytic strategy and conducted the data analysis. BHC and CH contribute the study design and prepare the Methods and the Discussion sections of the text, YHL and CHS helped conduct the literature review. All authors read and approved the final manuscript.

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Competing interests

The authors declare no conflict of interest.

Ethics approval

This study protocol was approved by the institutional review board of Chang Gung Medical Foundation (IRB 103-2572B).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

REFERENCES

1. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010;33:676.
2. Dornhorst A, Paterson CM, Nicholls JS, et al. High prevalence of gestational diabetes in women from ethnic minority groups. *Diabet Med* 1992;9:820-5.
3. Chodick G, Elchalal U, Sella T, et al. The risk of overt diabetes mellitus among women with gestational diabetes: a population-based study. *Diabet Med* 2010;27:779-85.
4. Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. *Diabetes Care* 2007;30(Suppl 2):P141-6.
5. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta- analysis. *JAMA* 2008;300:2754-64.
6. Stattin P, Björ O, Ferrari P, et al. Prospective study of hyperglycemia and cancer risk. *Diabetes Care* 2007;30:561-7.
7. Tong GX, Cheng J, Chai J, et al. Association between gestational diabetes mellitus

and subsequent risk of cancer: a systematic review of epidemiological studies. Asian Pac *J Cancer Prev* 2014;15:4265-9.

8. Bejaimal SA, Wu CF, Lowe J, et al. Short-term risk of cancer among women with previous gestational diabetes: a population-based study. *Diabet Med* 2016;33:39-46.
9. Powe CE, Tobias DK, Michels KB, et al. History of Gestational Diabetes Mellitus and Risk of Incident Invasive Breast Cancer among Parous Women in the Nurses' Health Study II Prospective Cohort. *Cancer Epidemiol Biomarkers Prev* 2017;26:321-7.
10. Park YM, O'Brien KM, Zhao S, et al. Gestational diabetes mellitus may be associated with increased risk of breast cancer. *Br J Cancer* 2017;116:960-3.
11. Dawson SI. Long-term risk of malignant neoplasm associated with gestational glucose intolerance. *Cancer* 2004;100,149-55.
12. Sella T, Chodick G, Barchana M, et al. Gestational diabetes and risk of incident primary cancer: a large historical cohort study in Israel. *Cancer Causes Control* 2011;22,1513-20.
13. Xie C, Wang W, Li X, Shao N, et al. Gestational diabetes mellitus and maternal breast cancer risk: a meta-analysis of the literature. *J Matern-Fetal Neonatal Med* 2017;7:1–11.

14. Chen YC, Yeh, H, Wu JC, et al. Taiwan's National Health Insurance Research Database: Administrative health care database as study object in bibliometrics. *Scientometrics* 2011,86,365-80.

15. Hsing AW, Ioannidis JP. Nationwide population science: lessons from the Taiwan National Health Insurance Research Database. *JAMA Intern Med* 2015;175:1527-9.

16. Kuzu OF, Noory MA, Robertson GP. The Role of Cholesterol in Cancer. *Cancer Res* 2016;76:2063-70.

17. Stocks T, Van Hemelrijck M, Manjer J, et al. Blood pressure and risk of cancer incidence and mortality in the Metabolic Syndrome and Cancer Project. *Hypertension* 2012;59:802-10.

18. Yang HP, Cook LS, Weiderpass E, et al. Infertility and incident endometrial cancer risk: a pooled analysis from the epidemiology of endometrial cancer consortium. *Br J Cancer* 2015;112:925-33.

19. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, et al. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. *JAMA Oncol* 2017;3:1683.

20. Lowrance WT, Ordoñez J, Udaltsova N, et al. CKD and the risk of incident cancer. *J*

Am Soc Nephrol 2014;25:2327-34.

21. Baumfeld Y, Novack L, Wiznitzer A, et al. Pre-Conception Dyslipidemia Is Associated with Development of Preeclampsia and Gestational Diabetes Mellitus. *PLoS One* 2015;10:e0139164.

22. Tobias DK, Chavarro JE, Williams MA, et al. History of infertility and risk of gestational diabetes mellitus: a prospective analysis of 40,773 pregnancies. *Am J Epidemiol* 2013;178:1219-25.

23. Sridhar SB, Xu F, Darbinian J, et al. Pregravid liver enzyme levels and risk of gestational diabetes mellitus during a subsequent pregnancy. *Diabetes Care* 2014;37:1878-84.

24. Mirghani Dirar A, Doupis J. Gestational diabetes from A to Z. *World J Diabetes* 2017;8:489-511.

25. Dehmer EW, Phadnis MA, Gunderson EP, et al. Association Between Gestational Diabetes and Incident Maternal CKD: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Kidney Dis* 2018;71:112-22.

26. Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. *Semin Cancer Biol* 2002;12:421-9.

27. Cohen JI. Epstein-Barr virus infection. *N Engl J Med* 2000;343:481-92.

28. Plouffe JF, Silva J, Jr, Fekety R, et al. Cell-mediated immunity in diabetes mellitus. *Infect Immun* 1978;21:425-9.

29. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM) FEMS *Immunol Med Microbiol*. 1999;26:259-65.

30. Berrou J, Fougeray S, Venot M, et al. Natural killer cell function, an important target for infection and tumor protection, is impaired in type 2 diabetes. *PLoS One* 2013;8:e62418.

31. Kumar M, Roe K, Nerurkar PV, et al. Impaired virus clearance, compromised immune response and increased mortality in type 2 diabetic mice infected with West Nile virus. *PLoS One* 2012;7:e44682.

32. Ljungberg B, Campbell SC, Choi HY, et al. The epidemiology of renal cell carcinoma. *Eur Urol* 2011;60:615-21.

33. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. *Nat Rev Urol* 2010;7:245-57.

34. Larsson SC, Wolk A. Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. *Diabetologia* 2011;54:1013-8.

35. Tseng CH. Type 2 Diabetes Mellitus and Kidney Cancer Risk: A Retrospective Cohort Analysis of the National Health Insurance. *PLoS One* 2015;11;10:e0142480.

36. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med* 2011;32:605-44.

37. Tseng CH. Diabetes but not insulin increases the risk of lung cancer: a Taiwanese population-based study. *PLoS One* 2014;9:e101553.

38. Solomon CG, Willett WC, Carey VJ, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. *JAMA* 1997;278:1078-83.

39. Troisi R, Weiss HA, Hoover RN, et al. Pregnancy characteristics and maternal risk of breast cancer. *Epidemiology* 1998;9,641-7.

40. Cnattingius S, Torrang A, Ekbom A, et al. Pregnancy characteristics and maternal risk of breast cancer. *JAMA* 2005;294,2474-80.

41. Brasky TM, Li Y, Jaworowicz DJ Jr, et al. Pregnancy-related characteristics and breast cancer risk. *Cancer Causes Control* 2013;24,1675-85.

42. Lawlor DA, Smith GD, Ebrahim S. Hyperinsulinaemia and increased risk of breast cancer: findings from the British Women's Heart and Health Study. *Cancer Causes Control* 2004;15,267-75.

43. Perrin MC, Terry MB, Kleinhaus K, et al. Gestational diabetes and the risk of breast cancer among women in the Jerusalem Perinatal Study. *Breast Cancer Res Treat* 2008;108,129-35.

44. Rollison DE, Giuliano AR, Sellers TA, et al. Population-based case-control study of diabetes and breast cancer risk in Hispanic and non-Hispanic White women living in US southwestern states. *Am J Epidemiol* 2008;167,447-56.

45. Aschebrook-Kilfoy B, Sabra MM, Brenner A, et al. Diabetes and thyroid cancer risk in the National Institutes of Health-AARP Diet and Health Study. *Thyroid* 2011;21:957-63.

46. Vigneri P, Frasca F, Siacca L, et al. Diabetes and cancer. *Endocr. Relat. Cancer* 2009;16,1103-23.

47. Chandrasekaran K, Swaminathan K, Chatterjee S, et al. Apoptosis in hepG2 cells exposed to high glucose. *Toxicol. In Vitro* 2010;24,387-96.

48. Zhang Y, Zhou J, Wang T, Cai T. High level glucose increases mutagenesis in human lymphoblastoid cells. *Int. J. Biol. Sci.* 2007;3,275-9.

49. Ategbo JM, Grissa O, Yessoufou A, et al. Modulation of adipokines and cytokines in gestational diabetes and macrosomia. *J Clin Endocrinol Metab* 2006;91:4137e43.

50. Wolf M, Sandler L, Hsu K, et al. First-trimester C-reactive protein and subsequent gestational diabetes. *Diabetes Care* 2003;26:819-24.

51. Leonardi GC, Accardi G, Monastero R, et al. Ageing: from inflammation to cancer. *Immun Ageing* 2018;15:1.

Table 1 Baseline characteristics

	Pregnancy women with GDM		Pregnancy women without GDM		P value
Number of population, n (%)	47373	(4.78)	943199	(95.22)	
Age, y, mean±SD		31.61±4.54		28.83±4.89	<.0001
Age group, n (%)					<.0001
≤ 20	407	(0.86)	45942	(4.87)	
21-30	18617	(39.30)	558108	(59.17)	
31-40	27203	(57.42)	329929	(34.98)	
41-50	1146	(2.42)	9220	(0.98)	
Comorbidity, n (%)					
Hypertension (ICD-9: 401-405)	1479	(3.12)	7743	(0.82)	<.0001
Dyslipidemia (ICD-9: 272)	1132	(2.39)	8197	(0.87)	<.0001
Liver disease (ICD-9: 070, 571)	3165	(6.68)	44509	(4.72)	<.0001
Infertility, female (ICD-9: 628)	8001	(16.89)	94405	(10.01)	<.0001
Kidney disease (ICD-9:582-3, 585-6, 588)	51	(0.11)	626	(0.07)	0.0008

GDM= Gestational diabetes; SD=Standard Deviation; ICD-9= International Classification of Disease, 9th Revision

Table 2 Hazard ratio (HR) of developing cancer in relation to baseline characteristics of study participants:

	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Patients				
GDM	1.421 (1.336-1.512)	<0.0001	1.197 (1.125-1.274)	0.0012
Non-GDM	1.0 (ref)		1.0 (ref)	
Age				
≤ 20	1.0 (ref)		1.0 (ref)	
21-30	1.627 (1.488-1.779)	<0.0001	1.581 (1.446-1.729)	<0.0001
31-40	2.843 (2.600-3.109)	<0.0001	2.678 (2.448-2.930)	<0.0001
41-50	4.883 (4.291-5.556)	<0.0001	4.479 (3.933-5.100)	<0.0001
Comorbidity, n (%)				
Hypertension (ICD-9: 401-405)	1.471 (1.291-1.677)	<0.0001	1.114 (0.976-1.272)	0.1101
Dyslipidemia (ICD-9: 272)	1.866 (1.648-2.113)	<0.0001	1.395 (1.229-1.583)	<0.0001
Liver disease (ICD-9: 070, 571)	1.573 (1.486-1.665)	<0.0001	1.432 (1.351-1.517)	<0.0001
Infertility, female (ICD-9: 628)	1.397 (1.340-1.457)	<0.0001	1.185 (1.136-1.236)	<0.0001
Kidney disease (ICD-9: 582-3, 585-6, 588)	2.077 (1.403-3.073)	0.0003	1.623 (1.095-2.404)	0.0159

HR=Hazard Ratio; GDM= Gestational diabetes; ICD-9= International Classification of Disease, 9th Revision

Table 3 Hazard ratio (HR) of the first cancer diagnosis between GDM group and non GDM group

(ICD-9 code)	Women with GDM (N=47373)		Women without GDM (N=943199)		Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Head and neck								
Oral & pharynx (140-1,143-6,148-9)	19	(0.04)	389	(0.04)	1.230 (0.776-1.950)	0.3792	1.105 (0.695-1.759)	0.6724
Nasopharynx (147)	90	(0.19)	1151	(0.12)	1.897 (1.530-2.351)	<.0001	1.739 (1.400-2.161)	<.0001
Digestive system								
Stomach (151)	18	(0.04)	256	(0.03)	1.703 (1.056-2.749)	0.0291	1.322 (0.816-2.142)	0.2570
Colorectum (153-4)	100	(0.21)	1705	(0.18)	1.420 (1.160-1.738)	0.0007	1.180 (0.963-1.447)	0.1099
Liver (155)	87	(0.18)	1393	(0.15)	1.504 (1.211-1.868)	0.0002	1.242 (0.998-1.545)	0.0521
Pancreas (157)	17	(0.04)	314	(0.03)	1.316 (0.808-2.145)	0.2699	1.072(0.655-1.755)	0.7807
Genital system								
Cervix uteri (180)	37	(0.08)	962	(0.10)	0.925 (0.666-1.285)	0.6429	0.903 (0.649-1.256)	0.5438
Uterus (179,182)	42	(0.09)	803	(0.09)	1.323 (0.970-1.805)	0.0768	1.051 (0.769-1.437)	0.7534
Ovary (183)	50	(0.11)	1146	(0.12)	1.061 (0.800-1.409)	0.6797	0.963 (0.724-1.280)	0.7928
Urinary system								
Urinary bladder (188)	9	(0.02)	162	(0.02)	1.387 (0.709-2.715)	0.3395	1.034 (0.525-2.033)	0.9236
Kidney (189)	25	(0.05)	245	(0.03)	2.573 (1.704-3.885)	<.0001	2.169 (1.428-3.293)	0.0003
Hematological system								
Leukemia (204-8)	11	(0.02)	359	(0.04)	0.742 (0.407-1.352)	0.3293	0.735 (0.402-1.344)	0.3169
Lymphoma (200-3)	19	(0.04)	596	(0.06)	0.771 (0.488-1.217)	0.2641	0.774 (0.489-1.226)	0.2754
Bone and connective tissue (170-1)	7	(0.01)	271	(0.03)	0.618 (0.292-1.309)	0.0708	0.582 (0.274-1.236)	0.1590
Lung and bronchus (162)	56	(0.12)	846	(0.09)	1.666 (1.271-2.184)	0.0002	1.372 (1.044-1.803)	0.0231
Skin (173)	15	(0.03)	201	(0.02)	1.834 (1.085-3.101)	0.0236	1.664 (0.980-2.825)	0.0594
Breast (174)	284	(0.60)	4373	(0.46)	1.654 (1.467-1.866)	<.0001	1.234 (1.093-1.393)	0.0007
Brain (191)	19	(0.04)	331	(0.04)	1.382 (0.870-2.195)	0.1703	1.232 (0.772-1.968)	0.3818
Thyroid (193)	91	(0.19)	1423	(0.15)	1.582 (1.279-1.956)	<.0001	1.389 (1.121-1.721)	0.0026
Other sites	91	(0.16)	1719	(0.18)	1.251 (0.989-1.583)	0.0619	1.154 (0.910-1.462)	0.2373
Total (140-208)	1063	(2.24)	18444	(1.96)	1.421 (1.336-1.512)	<.0001	1.197 (1.125-1.274)	<.0001

Model was adjusted for age, hypertension, dyslipidemia, liver disease, infertility, and kidney disease; HR=Hazard Ratio; GDM= Gestational diabetes; ICD-9= International Classification of Disease, 9th Revision

LEGENDS:

Figure 1: Flow chart for population selection

Figure 2: The cumulative incidence rates of any type of cancer in patients with or without GDM from the index date until the first occurrence of the cancer using Kaplan-Meier methods.

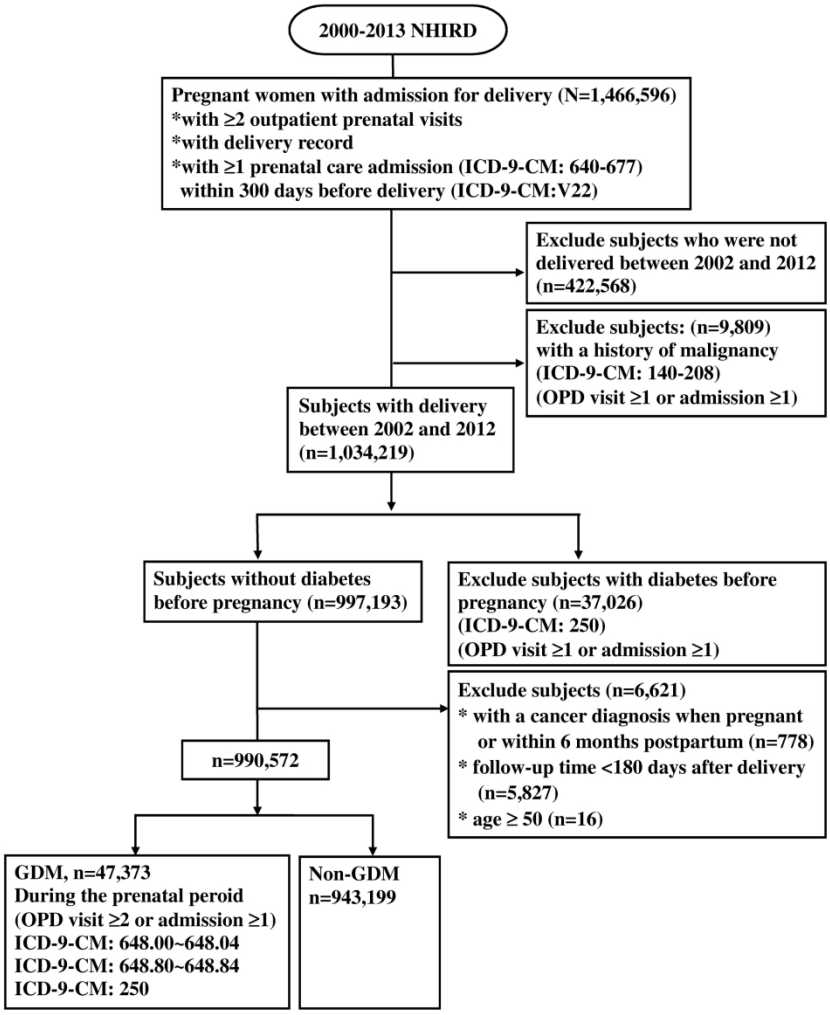

Figure 1

209x297mm (300 x 300 DPI)

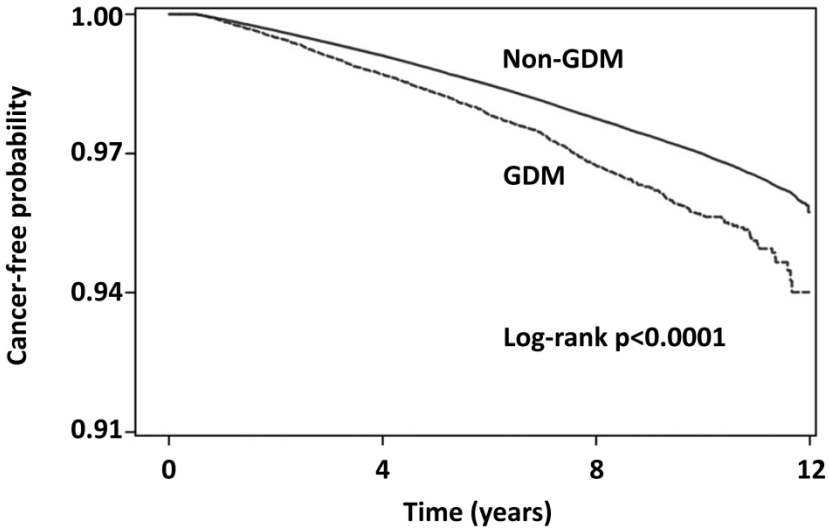

Figure 2

297x209mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10-11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-12
Bias	9	Describe any efforts to address potential sources of bias	10-12
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	10, See Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13,28-29
		(b) Indicate number of participants with missing data for each variable of interest	13
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-14, 28-30
		(*b*) Report category boundaries when continuous variables were categorized	13, 28
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13-14, 29-30
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13, See Fig 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.